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**Item: 6033**

# Data for Refining Anticipated Residue Estimates Used in Dietary Risk Assessments for Organophosphate Pesticides (Draft 3/26/99)

## Executive Summary

The Food Quality Protection Act (FQPA) of 1996 requires EPA to reassess all existing tolerances, based on available information, according to new, more stringent standards. Among these new standards are specific determinations regarding the potential for increased sensitivity of infants, children, and other subpopulations to the pesticide, assessment of the potential for aggregate exposures from various sources (such as the diet, drinking water and pesticide uses in and around the home) and cumulative assessments of pesticides with a common mechanism of toxicity. EPA anticipates that refinements, beyond those routinely applied to EPA's dietary exposure assessments, will be key to developing more realistic estimates of the actual residues on food as EPA proceeds through the aggregate and particularly the cumulative assessment of pesticides which have a similar toxic effect via a common mechanism of toxicity, for example, the organophosphates (OPs). Having more realistic estimates of residues ultimately improves the Agency's ability to make informed regulatory decisions that fully protect public health and sensitive subpopulations, including infants and children.

This document describes the types of data that can be used to refine residue estimates, outlines the basic characteristics of useful data, discusses how residue data and usage data are linked, and explains how EPA will use these types of data in its dietary exposure assessments. Bridging studies, which are used to quantify the difference in residues resulting from various application rates, are described in some detail. Also discussed are:

- residue decline studies, which can be used to quantify the differences in residues resulting from various pre-harvest intervals (PHIs);
- residue degradation studies, which characterize the decreasing amounts of residues over time;
- cooking and processing data;
- market basket data; and
- data to quantify residues in meat and milk after cooking and pasteurization.

Finally, interested parties may provide existing and available data of the types described in this document to EPA. The practical experience of working with existing data will enable the Agency to refine both current assessments and the guidance that is being developed for conducting new studies.

## I. Introduction

### Purpose

The purpose of this document is to outline the types of data the EPA can use to refine residue estimates for pesticides (especially the OPs), explain when and how these data may be used, and how such data may be submitted, if any interested parties wish to provide them to EPA. Many stakeholders -including commodity groups, food processors, and pesticide registrants- have indicated to EPA that they have information that more accurately characterizes actual pesticide use practices and actual residues, than the label information and anticipated residue factors that have been used by EPA. These groups would like the Agency to consider these data in its dietary risk assessments and in evaluating possible risk mitigation for specific pesticide uses. This information includes, for example, the range of residues resulting from various application rates and various pre-harvest intervals (PHIs), the percentage of pesticide used at various application rates, and the percentage of treated crops harvested at various intervals. Such data are often generated during efficacy and residue testing programs associated with product development. Other useful information that stakeholders may wish to provide would quantify the reductions in residues from storage, cooking and processing practices.

### Scope

This document is primarily intended to provide guidance for the submission of existing data and data currently under development and nearing completion related to the organophosphates (OPs). This effort focuses on the OPs because this group of pesticides is the first to be identified as having a common mechanism of toxicity that will require a cumulative exposure assessment. The types of data described in this document may also be used to refine residue estimates for chemicals other than OPs. However, at this time, EPA is most interested in information related to OPs.

While this document focuses on existing data, it is likely that additional data, such as bridging studies and residue decline studies, will be needed to substantiate and quantify the impact of risk mitigation proposals. For example, if a risk assessment indicates that dietary risks are unacceptable using a pre-harvest interval (PHI) of 3 days, and registrants propose increasing the PHI to 10 days, residue decline data would be needed to quantify the difference (reduction) in expected residues at the longer interval. In a similar way, if dietary risks are unacceptable with an application rate of 2 lbs. a.i./A and the registrants propose decreasing the rate to 1 lb. a.i./A, bridging studies would be required to quantify the difference in expected residues at the lower application rate.

### Related Guidance

EPA is preparing two related technical guidance documents, "Guidelines for the Conduct of Bridging Studies for Use in Probabilistic Risk Assessment" and "Guidelines for the Conduct of

Residue Decline Studies for Use in Probabilistic Risk Assessment," that will provide more detailed information. Additional guidance on the methods and types of data that can be used in dietary exposure assessments can be found in "Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs," which was issued for public comment in October, 1998 (63 FR 59780); EPA plans to make a revised document available in April, 1999.

## II. EPA's Current Approach to Refining Dietary Exposure Estimates

EPA has typically used a tiered approach to both acute and chronic dietary risk assessment. Generally speaking, the level of resources and data needed to refine exposure estimates increases with each tier. Lower tier (tiers 1 and 2) exposure assessments use tolerance levels and residues derived from guideline crop field trial data in addition to readily available usage information such as the percent of the crop that has been treated (PCT) with a particular pesticide. These assessments tend to overestimate actual pesticide residues in food at the point of consumption. If dietary risks are not of concern using lower tier exposure estimates, no further refinements are made. However, with aggregate and cumulative assessments now required by FQPA, it is likely that higher tier (tiers 3 and 4) exposure estimates will be needed. These higher tier assessments involve probabilistic techniques (e.g., Monte Carlo analyses) for acute assessments, and routinely refine pesticide residue estimates by incorporating available monitoring data, processing factors (e.g., washing or cooking data), market basket survey information, and other information that allows EPA to consider distributions of residue values.

Residue information submitted to the Agency to support registrations and determine tolerances represents maximum labeled application rates and minimum labeled PHIs. These "worst-case" conditions are used to ensure that tolerances are set at levels that encompass the highest residues that could be found. In the absence of reliable monitoring data, current procedures call for the use of these controlled field trial residue values (derived from maximum application rates and minimum PHIs) in exposure and risk assessments. Oftentimes, this is the only information which is available to the Agency for use in these assessments. The Agency recognizes that using residue data from only the maximum application rate and the minimum PHI in risk assessments may overestimate the actual residue on foods for a number of reasons. Chief among these are: not all applications occur at the maximum label rate; and some crops are treated long before harvest-in effect creating a longer PHI.

In cases where the registrant believes that the range of real-world use rates are significantly lower than maximum application rates or the range of real-world pre-harvest intervals are significantly greater than the minimum label PHI, it may be advantageous to incorporate this information into probabilistic (i.e., Tier 3 and Tier 4) acute exposure and risk assessments. ***This information can be incorporated, however, only if reliable usage data are available for determining what percentage of the crop is treated at which rate (and/or what percentage is harvested at which PHIs).*** Together, residue data collected from a series of reduced-use or multi-PHI field trials and information on real-world application rates or pre-harvest intervals

would enable EPA to incorporate the residue values resulting from the entire range of application rates and/or PHIs in the exposure assessment. The Agency emphasizes that both multi-rate and/or multi-PHI residue data specifically collected for this purpose and use/usage data are required to implement this refinement and that neither one, by itself, is sufficient. The reader is referred to a companion paper entitled, "The Role of Use-Related Information in Pesticide Risk Assessment and Risk Management" for further discussion of the sources of use and usage data and how EPA employs these data in its assessments.

Because pesticides have different physico-chemical and environmental fate properties, and these properties interact with other site-specific environmental conditions (e.g., soil type and pH, weather, etc.), it cannot simply be assumed, for example, that one-half of the maximum application rate or that twice the PHI will necessarily result in one-half of the residue.

In its review of EPA's guidance for probabilistic exposure assessments, the FIFRA Scientific Advisory Panel (SAP) supported the use of multi-rate, multi-PHI data in probabilistic assessments. However, the Agency has, so far, only minimal experience reviewing studies which deal quantitatively with the relationship between resulting pesticide residues and varying application rates or PHI's. We expect that a valid and reproducible quantitative relationship will more readily be established between residue level and application rate than it would be between residue level and pre-harvest interval. Accordingly, we are particularly seeking comment on this aspect of the notice and encouraging registrants to submit any pertinent data which may help elucidate this relationship and assist the Agency in developing these guidelines. As such, we also caution registrants that methodologies for establishing these quantitative relationships are still being developed and, in cooperation with USDA's IR-4, tested, and that the Agency is unable to state, at this time, than any information submitted or generated in response to this notice will necessarily be incorporated into our risk assessments.

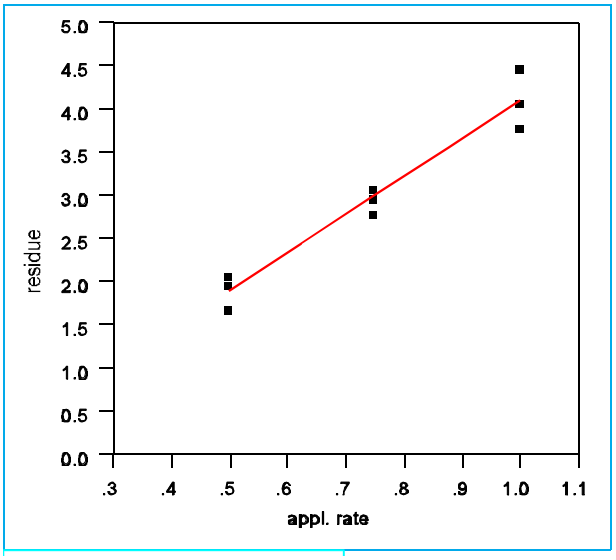
## III. What Additional Information Would Be Useful?

The types of data that can be used to refine residues estimates can be categorized as bridging, residue decline, residue degradation, cooking, processing and market basket studies. Each category is described in more detail below:

### Bridging Studies

Bridging studies are used to quantify the difference in residues resulting from various application rates. This type of study is intended to "bridge" pesticide residue concentrations between maximum application rates used to determine tolerances and the range of more typical rates at which the pesticide is actually applied. Generally, bridging studies consist of one or more field trials using several different application rates. The applications should occur at the same location and at the same time. They are used to establish the relationship between application rate

and resulting residue level. This information, together with use/usage information on what fraction of the crop is treated at each rate, permits the Agency to refine its estimates of exposure by incorporating residues resulting from the full range of application rates in its probabilistic assessments. An example of the results from a hypothetical bridging study is illustrated to the right. As can be seen, increasing application rate results in quantitatively increasing residues. This information, together with information on what fraction of the crop is treated at what rate, could be used to produce a distribution of residue values for use in a probabilistic assessment. Bridging studies and related usage information will influence the dietary risk assessment most when there are large differences between the maximum and typical application rates, and when a large percentage of the applications occurs at less than the maximum rate.




EPA is currently developing a detailed guidance document for conducting and evaluating bridging studies, as mentioned above. The following is a summary of key points that will serve as interim guidance for submission of bridging studies until the detailed guidance document is issued.

*Purpose , Required Location and Number of Field Trials*

Side-by-side field trials should be designed to compare residues resulting from maximum label conditions (i.e., those conditions used to derive a tolerance) to the range of typical application rates. Generally, EPA would need such comparative data from between one and three field trials, depending on acreage and geographic extent of production (as indicated in OPPTS Test Guidelines, Residue Chemistry, 860.1500, August 1996). Ideally, these field trials would be conducted at locations previously used to support the maximum label rate. The sites chosen should reflect different geographical regions, with one location representing the region with the highest proportion of production for a given crop, a second (if needed being the region where the highest average field trial (HAFT) value occurred for a given crop, and the third (if needed) being the region with the second highest production (see Tables in OPPTS Test Guidelines, Residue Chemistry, 860.1500, August 1996).

Data establishing relationships between residues and application rates should be derived from field trials conducted at the *same site* and the *same time* because of the potential impact of environmental conditions and variability in study conduct on results. Therefore, only data from controlled field trials specifically designed and collected to monitor the effects of application rate on residue should be used. For example, it would not be appropriate to attempt to derive a relationship between application rate and

resulting residues if data from one application rate were obtained from a field trial conducted in California in 1992 and residues from another application rate were obtained from a field trial conducted at the same or a different site three years later. Data provided should include weather and precipitation records to enhance the evaluation of a study and its results.

*Extrapolation of Results between Similar Crops*

Extrapolation of data for the same active ingredient between similar crops may be possible on a case-by-case basis, considering similar cultural practices and application patterns.

*Number of Different Application Rates*

Since the purpose of the field trials is to "bridge" the residues resulting from the maximum application rate to those representing more typical rate(s), one application rate in each field trial must be at the maximum label rate (i.e., that rate used to establish the tolerance). Residues at all other rates will be compared to residues at this maximum rate to establish the relationship between application rate and resulting expected residue concentrations. At least two other (generally lower) application rates should be selected (for a total of three rates) so that a quantitative relationship between application rate and residue level can be affirmed. The data should ideally include the maximum label rate, the minimum label rate, and at least one additional intermediate rate (preferably a "typical" rate or a rate mid-way between the maximum and minimum rates).

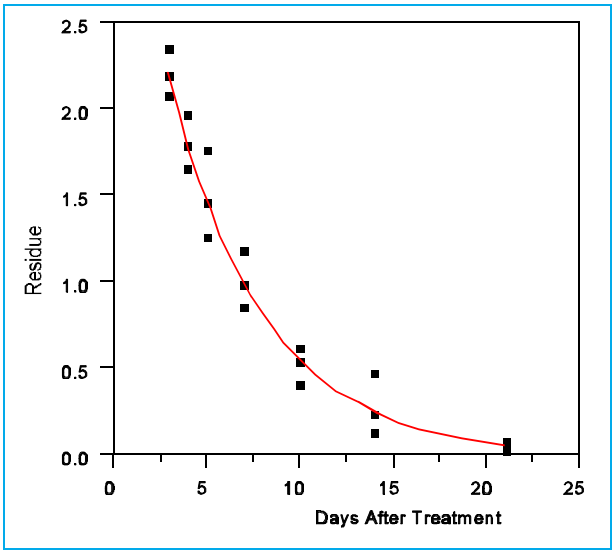
The Agency is willing to consider extrapolated application rate-residue level relationships. For example, if residues less than the level of quantitation (LOQ) are expected, it might be preferable to use exaggerated rates in the bridging studies in an attempt to determine the relationship between application rate and resulting residue level. Further, if minimal residues are expected at the maximum label rate, it may be advisable that the bridging study application rates consist of the full (1x) rate in addition to two other (exaggerated) rates (e.g., 1.5x and 2x).

*Number of Composite Samples to Collect at Each Application Rate*

For each of the bridging study trials, at least three independent samples should be obtained at each application rate. For example, if reduced rate field trials are being conducted with three potential application rates (e.g., ½x, 3/4x, and 1x), a total of at least nine composite samples (three at each rate) should be collected.

Finally, in order to be useful for risk assessment purposes, the bridging data must clearly demonstrate that reduced rates do result in quantitatively reduced residue levels.

## Residue Decline Studies




Residue decline studies recognize that not all crops are harvested at the labeled minimum pre-harvest interval (PHI). These studies are used to establish the relationship between the time of harvest (relative to the last pesticide application) and the level or amount of residues found on the commodity. Because pesticides dissipate at different rates, it cannot be assumed that this relationship would be the same for all chemicals. For example, doubling the PHI for one chemical may result in half the residue, whereas for another, more persistent compound, increasing the PHI may have little effect on the resulting residues. In a residue decline study, samples from one, two or three field trials are collected and analyzed at multiple pre-harvest intervals to determine rates of residue disappearance/dissipation. While a minimum of three intervals is needed, five or more would be preferable. A hypothetical example of results from a residue decline study is shown above. As can be seen, increasing days after treatment results in quantitatively decreasing residues. This information, together with use/usage information on what fraction of the crop is harvested at each interval, would permit the Agency to refine its estimates of exposure by incorporating the full range of harvest intervals. Residue decline studies and related usage information are most useful when there are large differences between the labeled and typical PHIs. Residue decline data could have significant impact on OP risk assessments because, in general, these compounds are relatively short-lived. Bridging and residue decline studies could be combined to better incorporate both multiple rates and multiple PHIs.

## Residue Degradation Studies

Some crops such as apples and potatoes can be typically stored for relatively long periods of time after harvest and before purchase by the consumer. Other items (e.g., tomatoes and bananas) may be typically picked green for ease of transport; of necessity, many days can, therefore, pass between harvest and consumption. Residue degradation studies are designed to characterize the decreasing amounts of pesticide residues over time on commodities during storage or transportation; they incorporate aspects of both residue decline and processing studies. In a residue degradation study, samples are collected before storage or transportation begins and at different points in the "process" which correspond to times that consumers may purchase the food.

## Cooking and Processing Data

Cooking and processing data permit better estimates of pesticide exposure by incorporating information on actual consumer and industry food preparation practices, such as

washing, peeling and various cooking methods.

The Agency recognizes that home processing (including washing, peeling, cooking, etc.) can significantly reduce exposure to pesticides. For example, potatoes would likely be cooked prior to consumption and oranges and bananas would be peeled. If information is available on how these practices affect residue levels in the *consumed* item, the Agency is willing to consider data which quantify these reductions. In a home processing/cooking study, residue measurements in the raw agricultural commodity are made prior to cooking/ washing/ peeling and again after cooking/washing/peeling. This reduction factor can then be incorporated into the risk assessment if there is additional information concerning the prevalence of these practices (e.g., 100% of potatoes are cooked prior to consumption, 100% of oranges are peeled prior to consumption).

Information on the effects of commercial food processing on pesticide residues would also be useful. In commercial processing studies, samples are collected at least two points in the processing procedures (e.g., before processing/cooking, after washing, after peeling, at the end of processing, etc.) and a processing factor (typically a large reduction) calculated. The processing practices used in the study must reflect typical commercial practices. For example, is the raw agricultural commodity typically washed, peeled, cooked or otherwise treated before canning, freezing, drying or other types of processing? How prevalent are these practices? Do these practices represent the industry as a whole or do they vary by region? (For example, are all canned tomatoes washed, peeled and heat processed in the same manner?) For comparison purposes, are residue data available to compare residues on commodities at various stages of processing-- as they come into the plant, after washing, and after peeling or cooking?

**Market Basket Data**

Market basket data are intended to characterize the difference between the level of residue that is found on commodities in the field and the residues that remain at the time of purchase by the consumer. Market basket surveys use statistically defined sampling procedures designed to produce residue data which can be directly used in a probabilistic assessment. Generally, samples are collected at the point of sale to the consumer (e.g., supermarkets or convenience stores). Samples may be prepared for consumption (e.g., peeled or washed). This type of data is particularly useful to characterize the actual residues on commodities that are typically consumed fresh as a single serving, for example, apples, oranges and tomatoes.

**Data to Quantify Residues in Meat and Milk After Cooking and Pasteurization**

One subset of processing data that may be particularly useful in refining residue estimates for organophosphate pesticides (OPs) is cooking and pasteurization data for meat and milk. In the process of reassessing tolerances for OPs, EPA has reviewed sufficient data for many OPs to determine that there is no expectation of finite residues in the meat, milk, poultry and eggs of animals fed agricultural products treated with those pesticides. Under 40 CFR 180.6 (a), tolerances need not be established in such instances. However, for some uses of OPs, particularly

dermal applications, finite residues are found in the tissues and milk of animals. Animals may be exposed to OPs through dermal applications whereby the OPs can be absorbed systemically into the animals and distributed to milk, fat, muscle, the liver, and the kidney as well as other organs or tissues. While there is variability among organophosphate pesticides in their ability to be absorbed through animal skin and ability to partition throughout animal tissues, the majority have at least some systemic bioavailability following dermal application, and partition to tissues that may serve as a potential source of human dietary exposure to these substances or their oxon metabolites.

In its assessment of human dietary exposure to OPs from consumption of meat and milk from animals treated dermally with OPs, EPA has considered the potential impact of food cooking/processing prior to consumption since the majority of all meat and milk consumed in the United States is cooked and pasteurized, respectively. In estimating dietary exposure to an OP, however, it is difficult for the EPA to include the effect of cooking or pasteurization on the pesticide since empirical stability data representative of these conditions are usually lacking. EPA conducted a literature search to investigate whether data were available on the effects of meat and milk processing on OP residues. Based on this search, the Agency believes that processing is likely to significantly decrease exposure to OP residues in meat and milk, but that specific studies to quantitatively determine the influence of cooking on OPs in beef and pasteurization on OPs in milk are needed before the Agency can incorporate anticipated declines in OP residue levels in its dietary exposure assessments. Such studies would not only apply to dermal applications of OPs to agricultural animals, but would also be relevant to oral exposure to livestock following ingestion of feedstuffs that contain OPs. If finite residues of an OP are found in meat and milk and if no data are available concerning the effect of cooking or pasteurization on those residues, then the Agency must assume that both meat and milk are consumed with residues present.

The Agency has identified specific data needs to help determine declines in OP residues in meat and milk through processing. These include:

- tests that more closely represent actual cooking of meat. This includes variations in temperature (e.g., those used to stew meat vs. those used to roast meat; type of cooking (grilling vs. boiling); and cooking duration (few minutes to several hours).

- tests that determine the pH ranges of meat prior to and during cooking. Since pH can significantly influence decomposition of OPs during cooking, a determination of the range of pH values that are likely to exist under the conditions mentioned in the preceding bullet is needed. (What is the pH of meat before cooking? Does it change during cooking? If so, how do these changes influence stability of a given OP?).

- tests that determine the stability of OPs in milk during batch process pasteurization. As a minimum, studies should be conducted at the minimum temperature of 63°C and the minimum time of 30 minutes required for this

process. Studies at higher temperatures and longer durations may also be needed.

- tests that determine the stability of OPs in milk during continuous process pasteurization. In the continuous process, milk is heated to a least 72°C for at least 15 seconds (this is often referred to as high-temperature-short-time (HTST) pasteurization). As a minimum, tests need to be conducted that determine OP stability under these conditions.

- tests that determine the stability of OPs in milk during ultra high temperature pasteurization. This pasteurization process involves a shorter time (2 seconds) and a higher temperature (minimum of 138°C) than the processes described above. Tests need to be conducted that determine OP stability under these conditions.

- testing on a large number of organophosphorus pesticides. To develop a more robust data set, all of the above testing needs to be conducted on a large number (at least 10) of structurally diverse pesticides.

- development (or further evaluation) of sensitive but simple methods that assay cholinesterase inhibitory activity.

EPA will provide guidance to any parties who plan to undertake any of the above referenced studies**.**

**Other Types of Information**

Most available monitoring data consist of composited samples which may not accurately reflect the entire range of residues that could be present in single-servings. For acute risk assessments and single-serving sized commodities, this variability in residues can be significant. The Agency is, therefore, particularly interested in single-serving analyses for those commodities which are typically consumed in single-serving sizes.

## IV. When and How Will EPA Use These Data?

EPA will consider existing data that are submitted in a timely manner, however, EPA cannot assure submitters that all data that are provided will be used in the OP risk assessments. The use of Good Laboratory Practices (GLP) is not essential for the submission of existing residue decline, bridging or residue degradation data. However, submitters must note in their cover letters whether or not the study was conducted in accordance with GLP. The submission should also address whether the data generated adheres to the spirit of GLP in that quality assurance (QA) and quality control (QC) measures have been taken from sample collection through analysis.

If data are deemed to be adequate for risk assessment purposes, they will be considered in

the on-going reviews of the OPs. The optimal time for considering these types of data is during the risk assessment revision following the first 60-day public comment period on the preliminary assessment. Data may also be used during the risk management phase to confirm that proposed risk mitigation is adequate. In some cases, assessments may not indicate dietary risks of concern for an individual OP. However, registrants or others may wish to develop data to further refine estimates prior to the cumulative phase of the OP assessment.

Studies or information should be submitted through normal document processing procedures (PR Notice 86-5). The transmittal letter should give an abstract or brief summary of the results of the study. A copy of the transmittal letter should be provided to the Chemical Review Manager (CRM) for the chemical in the Special Review and Reregistration Division.

**V. Questions/Issues for Public Comment**

1. EPA proposes to review existing bridging, residue decline and other data and to develop guidance for conducting these kinds of studies. The purpose of these multi-rate, multi-PHI studies is to be able to use the full range of expected residue values (based on the full range of application rates and PHIs) in dietary exposure assessments and thereby produce more realistic estimates of dietary risk. Is this a reasonable and efficient approach? What other approaches should EPA consider?

2. EPA believes that between one and three field trials conducted at different locations (with three different application rates at each field trial and three independent samples collected at each rate or PHI) are needed to demonstrate the mathematical relationship between application rate or PHI and amount of residue. Is this sampling regime adequate to characterize the range of potential residues?

3. In developing its guidance, EPA has assumed that the relationship between application rates and/or PHIs and resulting residue levels is not necessarily the same for all chemicals. Is there any information available to suggest that this assumption is incorrect? Is there any information available to suggest that the relationship between application rates and/or PHIs and resulting residue levels for the organophosphates as a class may be similar?

4. EPA is willing to consider data on the prevalence of food processing practices, along with data to quantify residue reductions from such practices. Should information on the extent of food processing practices be validated? If so, how could this be accomplished?